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Opioid Use in Pregnancy, Neonatal Abstinence Syndrome, and Childhood Outcomes: Executive Summary of a Joint Workshop by the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, American Congress of Obstetricians and Gynecologists, American Academy of Pediatrics, Society for Maternal-Fetal Medicine, Centers for Disease Control and Prevention, and the March of Dimes Foundation

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Abstract

In April 2016, the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development invited experts to a workshop to address numerous knowledge gaps and to review the evidence for the screening and management of opioid use in pregnancy and neonatal abstinence syndrome. The rising prevalence of opioid use in pregnancy has led to a concomitant dramatic fivefold increase in neonatal abstinence syndrome over the past decade. Experts from diverse disciplines addressed research gaps in the following areas: 1) optimal screening for opioid use in pregnancy; 2) complications of pregnancy associated with opioid use; 3) appropriate treatments for pregnant women with opioid use disorders; 4) the best approaches for detecting, treating, and managing newborns with neonatal abstinence syndrome; and 5) the long-term effects of prenatal opioid exposure on children. Workshop participants identified key scientific opportunities to advance the understanding of opioid use disorders in pregnancy and to improve outcomes for affected women, their children, and their families. This article provides a summary of the workshop presentations and discussions.

Opioid use has quadrupled over the last decade⁽¹⁾ with 259 million prescriptions in 2012 alone in the U.S., which consumes more prescription opioid pain relievers than any other nation.⁽²⁾ Approximately one-third of insured reproductive-aged women fill a prescription for an opioid medication each year.⁽³⁾ Every three minutes, a woman seeks care in an emergency department related to prescription opioid misuse.⁽¹⁾ Prescribed opioids that can be misused include codeine, fentanyl, morphine, opium, methadone, oxycodone, meperidine, hydromorphone, hydrocodone, propoxyphene, and buprenorphine.

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*For a list of invited speakers and participants, see Appendix 1 online at <http://links.lww.com/xxx>.

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Opioid use disorder is defined in the Diagnostic and Statistical Manual of Mental Disorders-5 as the repeated occurrence within a 12-month period of 2 or more of 11 problems, including: craving, tolerance, withdrawal, giving up important life events in order to use opioids, or an inability to cut down or control opioid use⁽⁴⁾ (refer to Table 1 in Schuckit et al [10]).

The increasing prevalence of opioid use in pregnancy has led to a concomitant fivefold increase in neonatal abstinence syndrome over the past decade, from 1.2 to 5.8 per 1000 hospital births.^(5, 6) Neonatal abstinence syndrome is a drug-withdrawal syndrome that opioid-exposed neonates experience shortly after birth. Since abstinence is different from withdrawal, using the term “neonatal opioid withdrawal syndrome” may be more appropriate. A recent analysis from the State of Tennessee found that two-thirds of neonatal abstinence syndrome cases were associated with legal prescriptions, and 28% of women enrolled in the state Medicaid program received at least one prescription for an opioid.⁽⁷⁾ By 2012, nearly 22,000 infants were born with neonatal abstinence syndrome in the U.S. each year, translating to one infant born every 30 minutes and resulting in \$1.5 billion in hospital charges nationwide.⁽⁵⁾

On April 4–5, 2016, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development convened a workshop entitled “Opioid Use in Pregnancy, Neonatal Abstinence Syndrome, and Childhood Outcomes,” co-sponsored by the American College of Obstetricians and Gynecologists, the American Academy of Pediatrics, the Society for Maternal-Fetal Medicine, the Centers for Disease Control and Prevention, and the March of Dimes, in which experts from diverse disciplines addressed research gaps in: 1) optimal screening for opioid use in pregnancy; 2) complications of pregnancy associated with opioid use; 3) the appropriate treatments for pregnant women with opioid use disorders; 4) the best approaches for detecting, treating, and managing newborns with neonatal abstinence syndrome; and 5) the long-term effects of prenatal opioid exposure on children. Workshop participants identified key scientific opportunities to advance the understanding of opioid use disorders in pregnancy to improve outcomes for affected women, their children, and their families.

Mechanism of Opioid Addiction and Pharmacology

Opioids bind to specific G-Protein Coupled Receptors in the brain to produce a pleasurable sensation. After the first identification of the mu receptor in 1973,⁽⁸⁾ delta, kappa, and nociceptin/orphanin FQ opioid receptors were identified. Opioids also depress respiration, potentially causing respiratory arrest and death. Opioid addiction is associated with compulsive drug-seeking behavior, physical dependence, and tolerance requiring higher doses to achieve the same physiologic effect. Inherited single nucleotide polymorphisms in the opioid receptor can reduce analgesia and potentially increase the likelihood of dependence.⁽⁹⁾

Once physical dependence has developed, withdrawal occurs if use is discontinued. For opioids with short half-lives such as heroin, withdrawal symptoms begin within hours after use and decrease greatly by day 4. For opioids with long half-lives such as methadone,

withdrawal symptoms may not begin for several days and decrease at about day 10. Drug cravings may persist for years, thus leading to high rates of relapse.(10)

Screening for opioid use disorder in pregnancy

Pregnancy may be the only time that a woman presents for medical care and when an opioid use disorder can be identified and treated. There are concerns about screening only selected groups of women. Chasnoff et al. found that rates of drug use among pregnant women in a Florida county did not vary by race, but the rate at which women were reported to social services for drug use was ten times higher in African-Americans compared to other groups. (11)

Use of a validated screening tool administered in a non-discriminatory, routine, and voluntary system would be optimal. The American College of Obstetricians and Gynecologists notes that: “Drug enforcement policies that deter women from seeking prenatal care are contrary to the welfare of the mother and fetus.” Instead, they urge their members to identify and refer patients already misusing drugs to addiction treatment professionals.(12) Unfortunately, as of 2016, only 19 states had drug treatment programs specifically targeted to pregnant women, while only 12 provide pregnant women with priority access to state-funded drug treatment programs.(13)

Women have a number of reasons to not disclose substance use in pregnancy, including legal ramifications, child custody issues, and the stigma.(14) The fear of consequences can actually discourage women from seeking prenatal care, placing both mother and fetus at higher risk of complications.(15) Whereas screening for prenatal alcohol use is generally well accepted, the validity, reliability, and clinical utility of standardized questionnaires to detect the use of illicit drugs during pregnancy have not been well established.(16)

There is disagreement between professional societies with regard to screening for substance use in pregnancy. The American College of Obstetricians and Gynecologists recommends screening all women for substance use before and during early pregnancy and providing an intervention when needed.(14) The U.S. Preventive Services Task Force has concluded that there is insufficient evidence to evaluate the benefits and harms of screening for illicit drug use in clinical populations including pregnant women.

Ideally, the experts at the workshop agreed that screening for substance use (alcohol, cigarette, illicit drugs, or prescription drugs without a prescription) during pregnancy should be universal. Women should be informed that these questions are asked of all pregnant women to ensure the mother and fetus receive the care they need and that the information will be kept confidential. Routine screening should rely on validated screening tools, such as the 4P’s (copyrighted and has to be purchased) and CRAFFT questionnaires (Car, Relax, Alone, Forget, Friends, Trouble screen for women aged 26 years or younger) (refer to Box 1 in ACOG Committee Opinion No. 524). (17) They can be used in direct interview format by physicians as well as non-physicians and can be streamlined into clinical practice by using computer-based approaches. Direct face-to-face questioning often leads to greater discussion of treatment need and available resources.

Testing biomarkers associated with exposure is a second screening approach. Laboratory detection of substance use has significant advantages, including objectivity, ability to test for multiple substances, widespread availability, and well-established validity.(18, 19) However, these tests may not be able to distinguish between occasional and regular use.(16) Furthermore, the short half-life of most substances and related metabolites limits urine detection to recent use only.(20) A negative test does not rule out substance use (especially if sporadic). False positive tests can occur with devastating consequences to the woman. When testing for multiple substances, analysis of hair provides an extended window of detection; (19) but testing of damaged hair may be unreliable, and the cost is prohibitive for large scale use. Urine testing has high specificity and positive predictive value depending on the assay and opioid drug being tested; it is relatively inexpensive, but sensitivity may be limited due to a short window of detection.(20)

The purpose of screening is to identify women with potential opioid use disorder and provide them appropriate care. Screening should be performed on a continuing basis, from the first prenatal visit to the puerperium. Laboratory testing is useful in conjunction with the interview and for referral into available treatment programs. Because biological assays are limited, awareness of the limitations of different assays is needed. Urine drug testing should be performed with the patient's consent and in compliance with existing state laws. Pregnant women should be informed of the potential consequences of a positive test prior to performing it, including any mandatory reporting requirements.(17)

Medication-Assisted Therapy

The impact of a comprehensive treatment plan for heroin addiction, including methadone maintenance and counseling for both patients and their partners, was first described in 1974. (21) The goals of treatment were to manage withdrawal, reduce cravings, and prevent illicit opioid use in the mother. Furthermore, in contrast to untreated heroin dependence, methadone treatment was associated with improved compliance with obstetrical care; higher neonatal birth weights; lower rates of fetal growth restriction, abruptio placenta, preterm birth, fetal mortality, and neonatal death; and a greater chance of the infant being discharged to his/her parents.(22–24) Zuspan et al. demonstrated in a single case with serial amniocentesis that low catecholamine levels in amniotic fluid during methadone treatment increased when the methadone dose was tapered, suggesting a fetal stress response with tapering.(25) Together, these data led to the recommendation for medication-assisted treatment for all women during pregnancy and to avoid detoxification due to the high rates of relapse, extreme stress, and unknown harm to the fetus.(17, 26)

Pregnant women can be initiated onto methadone either in a licensed outpatient methadone program(17) or as an inpatient. Methadone maintenance therapy, as prescribed and dispensed on a daily basis by a registered treatment program, is part of a comprehensive package of prenatal care, chemical dependency counseling, family therapy, nutritional education, and other medical and psychosocial services indicated for pregnant women with opioid use disorder. Once dose stabilization is achieved, patients continue to receive medication daily at outpatient methadone treatment facilities.

Obstetricians should communicate with the addiction treatment program whenever there are concerns about a patient's care and methadone dosage. The dosage should be adjusted throughout pregnancy if needed, especially in the third trimester to avoid withdrawal symptoms, including drug cravings, abdominal cramps, nausea, insomnia, irritability, and anxiety.(27)

Studies have been inconsistent in establishing a relationship between methadone dose and the incidence and/or severity of neonatal abstinence syndrome.(28–33) Methadone is usually initiated at 10–20 mg/day(34) and then titrated until the patient is asymptomatic in accordance with safe induction protocols (Table 1).(17, 35–43) Nearly half of women require a low daily dose (<60 mg), while the remainder are maintained initially on a medium (60–89 mg) or high dose (>90 mg).(27, 35) As pregnancy advances, the dose of methadone usually increases rather than remaining stable (8%) or decreasing (7%).(27) Increased dosing during pregnancy is expected because of physiologic increases in maternal intravascular volume and renal elimination during the second and third trimesters. Pregnant women with rapid metabolism may need twice-daily dosing to optimally control their symptoms.(44, 45) In a recent study, a mean methadone dose of 152 mg at delivery, divided into 2 to 6 doses per day resulted in 92% of mothers being illicit drug free at delivery and only 29% of neonates needing neonatal abstinence syndrome treatment.(46) An inadequate maternal methadone dosage may result in mild to moderate opioid withdrawal and cause fetal stress and increased likelihood for relapse.(47)

More recent evidence supports the use of buprenorphine for medication-assisted treatment during pregnancy. Buprenorphine is a partial mu-opioid receptor agonist that binds to opioid receptors with higher affinity but lower activity than complete agonists, such as methadone and heroin. Due to a decreased risk of overdose, buprenorphine inductions can occur in office-based settings prescribed by trained and approved physicians. This potentially increases the availability of treatment and decreases the stigma.(14, 38) Buprenorphine is typically taken once or twice daily with an average dose of 10 mg.(48) Because it is a partial mu-receptor agonist, buprenorphine has a ceiling effect at 32 mg, beyond which higher doses are not more effective.(36)

Buprenorphine improves neonatal outcomes compared to methadone therapy. The Maternal Opioid Treatment, Human Experimental Research (MOTHER) study, a multicenter, randomized controlled trial that compared buprenorphine to methadone treatment, examined maternal and neonatal outcomes for 175 mother-infant dyads. Buprenorphine-exposed neonates required 89% less morphine to treat neonatal abstinence syndrome and spent 43% less time in the hospital.(42) Maternal methadone was associated with a higher incidence of preterm labor and more respiratory distress in neonates at the time of delivery.(49) Furthermore, methadone-exposed neonates had higher neonatal abstinence syndrome scores(50) and required earlier treatment with morphine than buprenorphine-exposed neonates.(51) The total neonatal abstinence syndrome score and the individual signs of tremors, hyperactive Moro reflex, excessive irritability, and failure to thrive were significantly higher among methadone-exposed neonates than their buprenorphine-exposed counterparts.(50)

A meta-analysis compared 515 neonates whose mothers received methadone versus 855 neonates whose mothers received buprenorphine in 12 studies. The unadjusted neonatal abstinence syndrome treatment risk was lower (risk ratio = 0.90, 95% confidence interval (CI): 0.81, 0.98) and mean length of hospital stay shorter (−7.23 days, 95% CI: −10.64, −3.83) in buprenorphine versus methadone-exposed neonates. In treated neonates, neonatal abstinence syndrome treatment duration was shorter (−8.46 days, 95% CI: −14.48, −2.44) and total morphine dose was lower (−3.60 mg, 95% CI: −7.26, 0.07) in those exposed to buprenorphine. Buprenorphine exposed neonates also had higher mean gestational age and greater weight, length, and head circumference at birth. Fewer women treated with buprenorphine used illicit opioids near delivery (risk ratio = 0.44, 95% CI: 0.28, 0.70).(52)

The advantages of buprenorphine over methadone also include a lower risk of overdose(41) and the ability to be treated on an outpatient basis.(53) Disadvantages of buprenorphine compared to methadone include reports of hepatic dysfunction(36, 37, 54, 55) (although recent reports do not support any adverse effects on the liver), lack of long-term data on infant and child outcomes (including adverse effects), a non-significant yet clinically important dropout rate due to dissatisfaction with the drug or a more difficult induction with the potential risk of precipitated withdrawal.(56) Buprenorphine also has significant pharmacokinetic interactions with other drugs, including antiretroviral agents.(36, 57) Lastly, compared with methadone programs, the less stringent structure of buprenorphine treatment may make it inappropriate for some patients who require more intensive counseling and supervision.(58)

Overall, these results support the use of buprenorphine as a potential first-line medication for opioid-dependent pregnant women who are new to treatment. Both the World Health Organization and the American Society of Addiction Medicine support methadone and buprenorphine as medication treatment options for pregnant women.(58, 59) Practice guidelines for the use of buprenorphine during pregnancy are evolving; it is currently considered as a preferred treatment if a mother prefers buprenorphine to methadone, is willing to provide informed consent for treatment, and is capable of adhering safely to self-administration of the medication. Pregnant women on methadone maintenance therapy should not transition to buprenorphine, because buprenorphine may precipitate acute withdrawal.(59) The potential risk of unrecognized adverse long-term outcomes should be discussed with the patient. Methadone is the better option for women with long-standing, multi-substance abuse and previous failed attempts at detoxification.(35, 38, 59)

Buprenorphine is available as a single-agent product or in a combined formulation with naloxone, an opioid antagonist used to prevent diversion. Buprenorphine with naloxone is formulated to prevent injected use, because naloxone causes severe withdrawal symptoms when injected. During pregnancy, dosing with buprenorphine alone is recommended, although no maternal or neonatal adverse effects have been observed with use of the combination products.(60–63)

Naltrexone is a non-selective opioid receptor antagonist with potential to treat opioid use disorder in pregnancy by decreasing drug-seeking behaviors, drug cravings, and increasing treatment retention while eliminating the risk of neonatal abstinence syndrome.(64–66)

However, limited data are available on the safety and efficacy of naltrexone during pregnancy.(67, 68)

Interest has resurged in medically supervised withdrawal (i.e. detoxification) during pregnancy to prevent neonatal abstinence syndrome. Recent reports have described successful outcomes after medically supervised withdrawal during pregnancy in highly selected groups of women.(47, 69–73) Each of these studies has limitations, including high relapse rates of 50% and/or loss to follow-up. If medically supervised withdrawal is attempted, it should be conducted under the supervision of a physician experienced in perinatal addiction treatment.(70) A recent retrospective analysis of detoxification during pregnancy in 301 women with opioid use disorder in Tennessee reported outcomes of four non-randomized methods: acute detoxification of incarcerated patients (18.5% neonatal abstinence syndrome and 23.1% relapse rates); inpatient detoxification with intense outpatient follow-up (17.4% neonatal abstinence syndrome and 17.4% relapse rates); inpatient detoxification without intense outpatient follow-up (70.1% neonatal abstinence syndrome and 74.0% relapse rates); and slow outpatient buprenorphine detoxification (17.2% neonatal abstinence syndrome and 22.5% relapse rates).(73) Relapse was defined as a positive drug screen on admission, an admission by the patient at the time of delivery that she had relapsed, or a positive neonatal meconium test. It is important to note that neonatal abstinence syndrome is not the only outcome of interest, and it is unclear whether this approach is safe for the fetus and/or mother long-term. Intense behavioral health support and follow-up was essential for success without opioid use.

Despite the fact that subsequent cohort studies have not found a significant risk of fetal loss associated with medically supervised withdrawal during pregnancy,(47, 70) medication-assisted treatment is preferred over medically supervised withdrawal and is the standard of care for women with opioid use disorder in pregnancy. Medication-assisted treatment is associated with lower risks of maternal relapse to street drugs and improved compliance with prenatal care that outweigh the potential risks of neonatal abstinence syndrome.(17, 47, 58, 59, 67, 74) A list of local treatment programs for opioid use disorder can be found at the Substance Abuse and Mental Health Services Administration's web site (<http://dpt2.samhsa.gov/treatment/directory.aspx>).

Prenatal Care

Although observational studies suggest the possibility of an increase in relative risk for specific birth defects with opioid use (e.g., congenital heart defects, neural tube defects, gastroschisis), the absolute risk is low.(75, 76) Since these studies are limited by small sample size and confounding factors(17, 77) additional well-designed studies are needed. In a meta-analysis of three randomized controlled trials (n = 223) and 15 observational studies (n = 1923) that compared buprenorphine and methadone treatment in pregnancy no difference in the risk of congenital anomalies was identified. The authors concluded that the frequency and type of reported anomalies were similar to the general population, with no particular patterns noted by treatment group.(77)

Special considerations for prenatal care in women with opioid use disorder are summarized in Box 1.(35, 36, 78–81) These women have high rates of co-occurring mental health disorders – mood disorders, anxiety, and post-traumatic stress disorder,(82) as well as histories of physical and sexual abuse.(83) Polydrug use is common and the impact of other potential drug-drug interactions on the fetus are poorly understood. Some of these women have poor nutrition, other chronic illnesses, and limited social supports. Finally, all of the characteristics detailed above are associated with both poorer obstetrical outcomes and addiction treatment outcomes. Hence, pregnant women with opioid use disorder have a unique set of needs and treatment must address those needs.

Many pregnant women with opioid use disorder receive little or no prenatal care,(84) often due to applicable local and state laws and regulations. Only 40% of publically funded treatment facilities provide any women-centered services, and the number that provide prenatal or postpartum care has decreased from 19% in 2002 to 15% in 2009 despite a dramatic increase in need.(85)

Peripartum pain management

Providing adequate analgesia to opioid-dependent patients during labor and delivery is challenging, because cross tolerance to the analgesic effects of opioids and opioid-induced hyperalgesia results in increased sensitivity to painful stimuli.(86, 87) Special considerations for intrapartum care in women with opioid use disorders are summarized in Box 2. Studies show that women maintained on methadone or buprenorphine experience more pain following vaginal and cesarean delivery, and require more opioid analgesia following cesarean delivery than controls.(88, 89) It can be particularly difficult to provide adequate analgesia for women on higher doses of buprenorphine, because of its high affinity and partial agonist activity at the mu-receptor. As a result, higher doses of full mu-agonists are needed to displace buprenorphine, activate the receptor, and induce an analgesic effect.(87)

For labor analgesia, opioid dependence will not impact the efficacy of local anesthetics. Thus, epidural anesthesia or combined spinal-epidural analgesia often provide adequate pain relief. However, modern epidural analgesia generally includes low concentrations of local anesthetics (to minimize motor blockade) and short-acting opioids (e.g., fentanyl). Opioids are not fully effective in opioid dependent patients, which may diminish the effectiveness of epidural analgesia in some patients. Solutions with higher concentrations of local anesthetics or other non-opioid adjuvants (e.g., clonidine) may be necessary to achieve adequate analgesia. Patients who are unable to tolerate neuraxial anesthesia can be treated with short-acting opioids, titrated to effect. It is important to avoid treating opioid-dependent patients with mixed antagonists/agonists (e.g. nalbuphine or butorphanol), which are widely used for analgesia and pruritus, as these can precipitate withdrawal.(17, 36, 90, 91)

Adequate analgesia after vaginal delivery can generally be achieved with nonsteroidal anti-inflammatory drugs and acetaminophen, in combination with opioid maintenance therapy. However, acetaminophen is contraindicated in those with hepatitis C, which could affect up to 30% of opioid-dependent women.(49) Clinical protocols for non-narcotic pain management after delivery and discharge should include ice packs and analgesic creams.

For cesarean delivery, neuraxial anesthesia (i.e., spinal or epidural or combined spinal/epidural) is preferred. Postoperative pain control can be problematic. Intrathecal or epidural opioids can be administered, although they may not be fully effective for postoperative pain. Patient controlled analgesia can be used and titrated to effect with higher than usual doses required. Non-steroidal anti-inflammatory drugs and acetaminophen should be used. Use of gabapentin, transversus abdominis plane blocks, and intravenous acetaminophen may be opioid-sparing approaches that have utility in this setting, but more data are needed.

Generally, methadone should be continued at the usual dose throughout the peripartum period to avoid withdrawal. By the sixth postpartum week, 85% of patients remain within 10 mg of their methadone dose at delivery.(27) For buprenorphine, commonly used approaches include: continuing buprenorphine at the usual dose throughout the peripartum period; discontinuing buprenorphine at the time of admission to labor and delivery (particularly for planned cesarean deliveries) and substituting with either long-acting (e.g., MS Contin or fentanyl patch) or short-acting opioids (e.g., IR oxycodone or hydrocodone); or administering buprenorphine in divided doses (every 6 hours at 25% of maintenance dose to maximize the analgesic effects).(34, 38, 86, 87)

The postpartum patient who receives opioid therapy should be closely monitored for symptoms of over-sedation with dosages titrated as indicated. Other medications that can produce sedation (e.g., benzodiazepines and zolpidem) should be avoided to decrease the risk of respiratory depression.(86, 92) Data from non-pregnant subjects suggest treatment of acute postsurgical pain for patients on methadone therapy is not a risk factor for relapse.(87, 93) However, it is prudent to avoid “triggering” opioids (e.g., oxycodone), provide close follow-up, prescribe very limited quantities, and rapidly taper opioids by adding non-opioid alternatives. It is also reasonable to select opioids with the least euphoric potential for the treatment of acute pain.(94)

Lastly, of concern is the exposure of opioid-naïve patients to opioid medication after cesarean delivery. A recent survey of 667 post-cesarean patients conducted at six U.S. centers found that a median of 40 tablets were dispensed and 20 tablets were consumed.(95) Of those with leftover opioids, 93.2% had not disposed of the excess medication. This suggests that the amount of opioids prescribed following cesarean delivery generally exceeds the amount consumed by a significant margin and represents an important area of overprescribing. Recent data also suggest 1 in 300 opioid-naïve patients exposed to opioids after cesarean delivery go on to become persistent users.(96)

Postpartum care

Stresses associated with motherhood, newborn care, breastfeeding, and sleep deprivation can be overwhelming for patients with limited social support and resource availability, especially when infants are more irritable from neonatal abstinence syndrome.(97) Therefore, interventions designed to: a) improve rates and duration of breastfeeding; b) increase the use of hormonal and long acting reversible contraceptive methods; and c) identify and treat postpartum depression are necessary to improve outcomes for women with opioid use

disorder. Special considerations for postpartum care in affected women are summarized in Box 2.

Breastfeeding is particularly important for women with an opioid use disorder and their newborns, because it is associated with decreased severity of neonatal abstinence syndrome, increased maternal confidence, stress reduction, and enhanced maternal-child bonding.(98–101) Compared to formula fed infants, breastfed infants are less likely to need pharmacologic treatment for neonatal abstinence syndrome. If treatment is required, breastfed infants require lower doses of morphine and thus have shorter hospital lengths of stay.(102–105) Breastfeeding may also enhance compliance with medication-assisted treatment and be protective against illicit drug use.(99) The American Academy of Pediatrics recommends breastfeeding for women taking methadone or buprenorphine, regardless of maternal dose as very little methadone (1–3% of the maternal weight-adjusted dose) and minimal buprenorphine (<1% of the maternal weight-adjusted dose) is present in breastmilk.(99–101, 106–108)

Despite recommendations, breastfeeding rates among women on methadone range from 24–46% and as many as 60% of those who initiate breastfeeding stop after 6 days.(109, 110) In contrast, breastfeeding initiation rates reach 76% in women on buprenorphine, with 66% still breastfeeding at 6 to 8 weeks postpartum.(111) Due to significantly improved maternal and neonatal outcomes, women adherent to methadone or buprenorphine maintenance treatment should be encouraged to breastfeed unless there are specific reasons not to do so (e.g. HIV infection, other illicit drug use).(100, 101, 108, 112, 113)

Over 86% of pregnancies conceived by women with opioid use disorder are unintended, compared to 31–47% of pregnancies in the general population.(114, 115) Women also report a higher pregnancy rates with 29% reporting six or more pregnancies and 6% reporting ten or more pregnancies.¹¹⁵ A lack of awareness about available family planning services, mistrust of health care providers, ongoing illicit drug use, and lack of transportation and childcare create significant barriers to accessing family planning services.(116, 117) In evaluations of contraceptive use, 25–75% of sexually active women with an opioid use disorder reported no contraceptive use.(118–121) Even among women using contraception, approximately two-thirds of women report using condoms.(115, 120, 121)

Highly effective postpartum contraception is critical to avoiding unintended pregnancy. Long-acting reversible contraception, such as intrauterine devices and subdermal implants, effectively prevent unintended pregnancies and should be promoted over alternative methods due to enhanced compliance.(121–123) Use among women with opioid use disorder ranges from 2–29%.(121) Long-acting reversible contraception insertion in the immediate postpartum period, prior to patient discharge after delivery, should be considered to reduce barriers such as poor compliance with the postpartum visit.(124, 125) Efforts to incorporate comprehensive family planning services for women and their partners into opioid use disorder treatment programs are also desirable.

Access to adequate postpartum psychosocial support services, including chemical dependency treatment and relapse prevention programs, should be ensured. The prevalence

of anxiety and depression in pregnant women with an opioid use disorder range from 65–73% and more than 12% of women report suicidal thoughts.(82, 126) Women who report psychiatric symptoms often have greater addiction severity, are more likely to have deficits in family/social functioning, and are more likely to discontinue opioid use disorder treatment programs.(82, 127) Poor social support, low income, and education further place pregnant women with an opioid use disorder at significant risk for postpartum depression.(128) Incorporation of perinatal psychiatric screening and treatment within opioid use disorder treatment program settings are needed.

Neonatal abstinence syndrome and child health outcomes

In the 1970s, neonatal signs of withdrawal from methadone were reported as neonatal abstinence syndrome. In 1975, Finnegan and Lipsitz published their individual neonatal abstinence syndrome scoring systems that are still routinely used today.(129, 130) Subsequently, withdrawal from buprenorphine and OxyContin were reported in 1997 and 2002 respectively. Both licit (prescription of opioid-containing pain relievers) and illicit (e.g., heroin) maternal opioid use as well as the use of maternal medication-assisted treatment puts infants at risk for developing neonatal abstinence syndrome. In infants exposed to methadone, signs of neonatal abstinence syndrome usually appear within 3–5 days of birth, but may appear as late as a week of age, and last from days to weeks and rarely months of life. Infants exposed to buprenorphine who develop neonatal abstinence syndrome generally develop symptoms by 48 hours of life, peaking at 72–96 hours.(50)

Neonatal abstinence syndrome is characterized by hyperactivity of the central and autonomic nervous systems. Individual signs include dysfunction in the: central nervous system (irritability, high pitched cry, tremors, hypertonia, hyperreflexia, sleep disturbances); gastrointestinal system (regurgitation, loose stools, dysrhythmic sucking and swallowing, poor feeding, weight loss); respiratory system (tachypnea); and the autonomic nervous system (sweating, sneezing, yawning, nasal stuffiness, hyperthermia).

Assessment should consider the spectrum of neonatal abstinence syndrome signs that describe how the infant functions in each specific neurobehavioral domain, i.e., from no signs or dysregulated behavior, to mild, moderate, and severe dysregulation.(131) Optimal assessment should involve examination of the overall neurobehavioral functioning of the infant. Different substances (e.g. psychotropic medications, other illicit drugs) may have their own withdrawal syndrome and/or can potentiate opioid-induced neonatal abstinence syndrome. There is currently no method to assess the impact of other psychoactive substances on neonatal abstinence syndrome, as scoring tools are designed primarily for opioid-exposed infants.

All infants born to women who use opioids during pregnancy should be monitored for symptoms of neonatal abstinence syndrome for at least 5 days to determine if they are exhibiting signs significant enough to require treatment.(132) It is essential to identify the opioid-exposed mother-infant dyad antenatally or soon after birth to prevent early hospital discharge, promote breastfeeding (if safe to do so), assess the need for non-pharmacologic interventions (swaddling, rooming in), observe for the need for pharmacotherapy, and

coordinate necessary help for the mother. Using a scoring system to assess neonatal abstinence syndrome is most efficient and feasible in a busy clinical setting. There have been six Neonatal Abstinence Scores published between 1975–2009: The Finnegan Neonatal Abstinence Scoring Tool (FNAST) 1975;(129) the Neonatal Drug Withdrawal Scoring System 1975;(130) Ostrea Tool 1975;(133) the Neonatal Narcotic Withdrawal Index 1981;(134) the Neonatal Withdrawal Inventory 1988;(135) and the Maternal Opioid Treatment: Human Experimental Research Study Score (modified Finnegan).(136) Specific recommendations on their use are available for some scores with instructions to assure inter-rater reliability. The key issues in scoring should be: decide on which score to use; have a protocol on how to administer it; and provide continuous training to assure inter-rater reliability. There are ongoing studies designed to simplify the application of the Finnegan scoring system, as well as developing alternative physiologic assessments that may more accurately define when an infant with neonatal abstinence syndrome requires treatment and can wean off that treatment.

Not all infants exposed to antenatal opioids will develop significant signs of withdrawal. Environmental factors can certainly increase the incidence and severity of neonatal abstinence syndrome. These include exposure to CNS active agents such as: nicotine in cigarette smoke, benzodiazepines, gabapentin, selective serotonin reuptake inhibitors, and marijuana.(7, 137) There is also some evidence to indicate that genetic and epigenetic factors also affect neonatal abstinence syndrome severity in some infants.(138, 139) Further studies are needed to better define the genetic/epigenetic and the environmental risk factors that contribute to the incidence and severity of neonatal abstinence syndrome.

Optimal assessment of the infant with neonatal abstinence syndrome has not been definitively established. Current tools are subjective in nature and are designed for opioid-exposed infants born at term. They do not apply well to preterm infants, older infants, or polysubstance exposed infants. Infant assessment should also include an assessment of the mother/caregiver and the environment, which is not standard today. Appropriate neurobehavioral or non-pharmacologic interventions may reduce the severity of neonatal abstinence syndrome by decreasing infant stress and promoting infant self-regulation and development.(140) These interventions should be instituted prior to the initiation of drug treatment and may be successful in avoiding the need for pharmacologic therapy. The infant with neonatal abstinence syndrome is best managed in a calm environment (not guaranteed in a busy NICU) by specially trained personnel. Scoring systems that are used to decide if an infant requires pharmacotherapy may not accurately reflect the infant's functioning and regulatory capacity. A comprehensive understanding of the infant is necessary for the optimal treatment of neonatal abstinence syndrome, i.e., to decrease sensory overload, mitigate irritability, minimize uncontrolled body movements, and address specific problems with sleep, feeding and interaction.(141)

The incidence and the treatment of neonatal abstinence syndrome have a high level of variability (depending on multiple factors), with up to 80% of opioid-exposed infants in some studies requiring pharmacologic interventions.(142) Neonatal care is summarized in Box 3. Opioid medications are recommended when the neonatal abstinence syndrome score reaches a moderate level, and the infant cannot be managed by supportive measures alone.

(132) Once treatment is initiated, adherence of all providers to a standardized protocol appears to improve treatment outcomes (length of hospital stay, duration of pharmacologic treatment, cumulative dose, and number of treatment drugs) more than the choice of drug or the specific treatment protocol.(143) Based on published data through 2012, the American Academy of Pediatrics recommends commencing pharmacologic treatment with oral morphine or methadone, with preservative free formulations recommended. However, the optimal initial drug of choice remains unknown and is currently under study. When an infant reaches a maximal dose of a first-line medication, a second-line medication (e.g. phenobarbital or clonidine) is typically added. Just as first-line medications and dosing have not been well studied, second line drugs have even less data to support their use.

Rational pharmacotherapy should use the minimum dose of drug necessary to achieve treatment goals. Treatment is often initiated based on the weight of the infant, the severity of symptoms, or optimally a combination of both. Steady-state drug levels are needed to achieve the desired treatment effect and are a function of the dose, dosing interval, and half-life of the drug. It may be appropriate to use a loading dose or administer additional doses at the start of treatment to achieve a steady state level more rapidly rather than increasing the daily dose if an infant does not respond in a timely fashion. It is important to subscribe to the principle that the goal of therapy is not to generate very low neonatal abstinence syndrome scores, as the risk/benefit ratio of this approach has not been established. Treatment is considered adequate if the infant has rhythmic feeding and sleep cycles and optimal weight gain. Comprehensive treatment goals are four-fold: 1) support vital infant functions and development (nutrition, sleep, social interaction); 2) initiate family bonding (integrated care, breastfeeding if possible); 3) prevent complications (dehydration, weight loss, skin breakdown, inadequate rest, CNS hyperactivity, seizures); and 4) educate the family and provide adequate medical and social resources for the infant and family after discharge, as some infants will still be irritable and have increased needs despite being weaned off medical therapy.

There is a lack of evidence on the long-term effects of prenatal opioid exposure. Most studies were conducted prior to the start of the current opioid epidemic and have not included addiction related to prescription drug use. In addition, the long-term outcome of infants with neonatal abstinence syndrome is virtually unknown as these infants were typically embedded within more general studies of infants with *in utero* opioid exposure and most studies followed infants for only a few years. In general, findings from the follow-up literature on infants with prenatal opioid exposure are inconsistent.(43) For example, earlier studies have not found significant differences in cognitive development between children exposed to methadone in utero when followed to 5 years of age compared to control groups matched for age, race, and socioeconomic status. However, scores were often lower in both groups compared with data from the general population. In other studies, a number of cognitive, motor, and behavioral deficits were identified, such as lower IQ scores and poor social skills. Sample sizes were small and thus could not account for multiple confounding factors, such as polydrug use, environmental exposures, and poverty. Subject retention rates were poor and identifying appropriate comparison groups was problematic. In a meta-analysis only 5 studies were identified that reported quantitative effects of prenatal opioid exposure on child neurobehavioral outcome.(144) Preventive interventions that focus on

enriching the early experiences of such children and improving the quality of the home environment are likely to be beneficial.

DISCUSSION

A coordinated, multisystem approach best serves the needs of pregnant women with opioid use disorders and their infants. Key knowledge gaps have been identified with additional research needed to improve outcomes for women with opioid use disorder and for their infants (Box 4. Obstetric research is needed that focuses on optimal screening, treatment, and care throughout pregnancy and the postpartum period as well as elective maternal medically supervised withdrawal during pregnancy. Neonatal focused research needed includes: 1) a new scoring tool that incorporates a neurobehavioral assessment of the substance exposed infant's functioning as well as the need for pharmacologic management; and 2) optimal approaches to non-pharmacologic and pharmacologic therapy when needed. There are extremely limited data on childhood outcomes; well-designed studies accounting for the complexity of in utero and postnatal exposures are urgently needed. Additionally, basic science research using animal models of prenatal opioid exposure are useful to identify potential neurodevelopmental consequences following *in utero* exposure. Research to understand the genetic and epigenetic predisposition to tailor prevention and treatment interventions is needed. Lastly, training of health care providers in a manner that fosters multidisciplinary care and crosses specialty area boundaries is needed to provide optimal care to pregnant women with opioid use disorders and their infants.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Precis

Addressing gaps in screening and management of opioid use in pregnancy and neonatal abstinence syndrome is needed to combat the substantial increase of these conditions.

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Box 1**Prenatal Care for Women With Opioid Use Disorder****Prenatal Counseling Regarding Risks**

- Birth defects: Absolute risk is low — some evidence for increased risk in studies with small sample sizes and potential confounding
- Fetal growth restriction: Increased risk of association based on strong evidence
- Preterm birth: Increased risk of association based on strong evidence

Comorbid Conditions Screening

- Screen/test for:
 - Chronic pain conditions
 - Sexually transmitted infections
 - Infectious diseases (HIV, hepatitis B, and hepatitis C at initial visit and repeated in the third trimester, if indicated)
 - Liver function tests
 - Electrocardiogram prior to starting methadone (causes prolongation in QT interval)
- Concomitant medications (SSRIs, benzodiazepines, antipsychotics)
- Multi-substance use (alcohol, tobacco, marijuana)

Psychosocial Care

- Comprehensive assessment of mental health, screening for PTSD, depression, anxiety, bipolar disease, other psychiatric disorders
- Social conditions (intimate personal violence, unstable housing, lack of social support, partner-use, food insecurity, employment, education, parenting, legal issues)
- Residential treatment

Obstetrician–Gynecologist Prenatal Care

- Antenatal testing only if other clinical indication arises; eg, fetal growth restriction — lack of evidence for need for Opioid Use Disorder OUD alone
 - Perform at least 4–6 hours after the woman takes her daily maintenance methadone dose (reduce false-positive rate of nonreactive nonstress test or nonreassuring Biophysical profile)
- Ultrasound screening
 - 18–20 weeks anatomy ultrasonogram

- Serial fetal growth assessment
- Multi-specialty prenatal care needed
 - Anesthesia consult
 - Neonatology/pediatrics consult

SSRIs, selective serotonin reuptake inhibitors; PTSD, posttraumatic stress disorder;

Box 2**Intrapartum and Postpartum Care for Women With Opioid Use Disorder****Pain Management Intrapartum**

- Train labor and delivery and postpartum staff in appropriate pain control
- Doula may be helpful, if available
- Medication-assisted treatment: Continue maintenance dosing during hospitalization
- Medications:
 - Avoid mixed antagonist/agonist narcotics (eg, butorphanol, nalbuphine, and pentazocine)
 - Early epidural
 - Neuraxial anesthesia
- Alternative pain management
 - Mindfulness training, relaxation training
 - Gabapentin, ketamine, transversus abdominis plane blocks
 - Nitrous oxide

Postoperative Pain Management

- Cesarean delivery: Patient-controlled analgesia ; scheduled regimen of NSAIDs/acetaminophen
- Vaginal delivery: NSAIDs and topical analgesics preferred
- Judicious prescribing of short-acting opioids post–cesarean delivery, short follow-up
- Anxiety management: Be cautious with co-administration of benzodiazepines, as this can lead to respiratory depression
- Avoid trigger medications (eg, oxycodone) postpartum

Postpartum Support

- Allied health professionals may be used to provide in-depth, consistent follow-up
- Storage and disposal of leftover opioid medicine
- Social services consultation: Assess custodial care for the baby/other children
- Contraception counseling: Encourage long-acting reversible contraception
- Lactation counseling to encourage and support breastfeeding

NSAIDs, nonsteroidal anti-inflammatory drugs.

Box 3**Neonatal Care for Infants of Women With Opioid Use Disorder****Assessment for Neonatal Abstinence Syndrome**

- Scoring tools
 - Optimal assessment for infants with NAS has not been defined
 - Tools are subjective/highly variable
- Assessment period
 - Optimal timing of assessments as fewer symptoms in the first 24–96 hours
 - Depends on opioid metabolism and potential drug/drug interactions (polypharmacy)
 - Late onset possible (e.g. 2 weeks) – uncommon, but does exist
 - Rooming-in and more direct family involvement vs. remaining in the nursery for more continuous observation and assessment
- Factors affecting development and severity of NAS
 - Gestational age – preterm vs. term; birthweight
 - Methadone vs. buprenorphine - variability in PK/PD in neonates
 - Rooming in which promotes kangaroo care and breastfeeding
 - Tobacco smoking
 - Benzodiazepine exposure
 - Selective serotonin reuptake inhibitors exposure
 - Genetic predisposition

Treatment of Neonatal Abstinence Syndrome

- Need to standardize protocols and establish best practices (standard of care)
- Individualized to the infant and mother, hospital, and/or home environment
- Input from social services for predischarge/postdischarge treatment and follow-up
- Optimal pharmacologic approach unknown, but opioids recommended as first-line drugs
- When maximal dose achieved (which has not been well-established) without control of symptoms, a second or even third line agent may be needed (clonidine, phenobarbital)
 - Some medications contain alcohol and other preservatives with potential toxicities

- Goal of treatment - adequate sleep, feeding, weight gain, and physiologic functions
- Need staffing requirements studies (day-to-day care, staff ratios, rooming-in)

Neonatal Discharge and Follow-up

- Best place/environment for infants with NAS
 - Create programs that work with the mother-infant dyad, especially if the mother is in a substance abuse treatment post-partum
 - Regional variability in resources, requirements, and populations
- Educate parents (mothers and fathers) in special needs for infants with NAS
- Home weaning protocols and follow-up
 - 10% of infants discharged on phenobarbital for prolonged periods of time
 - High variability in weaning; lack standard monitoring and dosing changes
 - More likely to be re-hospitalized – coordinate services to avoid it

NAS, neonatal abstinence syndrome.

Box 4**Research Gaps and Opportunities**

Basic Science	<ul style="list-style-type: none"> Opioid use disorder is a syndrome commonly associated with multiple potentially deleterious exposures other than opiates and several adverse pregnancy outcomes including poor fetal growth, preterm birth, fetal loss, stillbirths and birth defects. <ul style="list-style-type: none"> ○ It is unlikely that the associated adverse pregnancy outcomes will be scientifically rigorously attributable to individual exposures among the numerous exposures that are characteristic of the syndrome. ○ Many covariates (exposures) that are strongly associated with opiate use include tobacco, alcohol, benzodiazepines, cocaine and other substances of abuse, poor nutrition, anemia, STIs, un-planned and un-desired pregnancies, poor educational attainment, low socio-economic status, poor housing conditions, exposure to and legitimate fear of violence ○ Absent scientifically rigorous data on causation, how should potentially deleterious exposures be prioritized for interventions? ○ Are there undiscovered mechanisms of adverse biologic effects on placental function of potentially deleterious exposures? What are the developmental and inherited genetic variations in opioid action and metabolism?
Prenatal Screening for Opioid Use Disorder	<ul style="list-style-type: none"> What is the best method for screening? <ul style="list-style-type: none"> ○ Modality (computer questionnaire, in person interview (with whom), biological sample) ○ Optimal time, interval, and frequency ○ Optimal tool (5Ps, SUR-P, etc.) ○ What are the barriers to screening (real and perceived)? How to maintain confidentiality and trust while minimizing judgmental behavior and punitive implications?
OB/Gyn Prenatal Care	<ul style="list-style-type: none"> How best to structure comprehensive care to bring all resources to women? What is optimal assessment for fetal well-being?
Medication-Assisted Treatment and Detoxification	<ul style="list-style-type: none"> What is the best technique to engage women in treatment? <ul style="list-style-type: none"> ○ Include women recovering from opioid use disorders? ○ Develop a screening tool to predict probability of relapse. ○ Will physiologic measures of opioid withdrawal be more useful than simply assessing cravings? What are the optimal safety, efficacy, and treatment approaches during pregnancy? <ul style="list-style-type: none"> ○ Methadone vs. buprenorphine ○ Combinations (buprenorphine + naloxone, naloxone, or naltrexone)

	<ul style="list-style-type: none"> ○ Impact of other agents (e.g. psychotropic medications, “mood stabilizers”) • Can “precision medicine” inform the appropriate dosing for all medications throughout pregnancy? Post-partum? During breastfeeding? <ul style="list-style-type: none"> ○ Which medication works best for which patients? ○ Need pharmacokinetic/pharmacodynamics studies for all medications during pregnancy and with breastfeeding ○ Need test for mother’s metabolism (fast vs. slow metabolizers) – may need different dosing schedules • How long do patients need medication? What is the best way to wean them? • Is there a sub-group of women with opioid use disorder who will be successful with detoxification therapy? <ul style="list-style-type: none"> ○ Can we reliably identify them <i>a priori</i>? ○ Need evidence for optimal fetal assessment and efficacy in this scenario ○ Role of benzodiazepines and adjunct medications (e.g., adrenergic blockade) with respect to success ○ Need medical interventions for known consequences of detoxification ○ Need trials of opioid detoxification with fetal monitoring and excellent follow-up, analyzed by intent to treat ○ Anticipate and minimize potential relapse rates if detox is undertaken • Understand the pathophysiology of detoxification during pregnancy: maternal, uteroplacental function, and fetal effects
Pain management intrapartum	<ul style="list-style-type: none"> • Optimal/appropriate agonist dosing <ul style="list-style-type: none"> ○ Integration of narcotic and non-narcotic medications ○ Effect modifiers (e.g., poly-drug use, smoking, and stress)
Pain management postoperative	<ul style="list-style-type: none"> • Comparative effectiveness of non-opioid alternatives for post-cesarean pain control (e.g., gabapentin, transversus abdominis plane block, IV acetaminophen) • Education and changing physician practices in postpartum pain management • What is the risk of overdose in those using illicit opioids or on high-dose chronic opioid therapy? <ul style="list-style-type: none"> ○ Is pregnancy an independent risk factor for overdose? If so, is it mediated by sleep-disordered breathing? • Post-cesarean opioid use. How to align the amount of opioid medication prescribed with what is needed? Implications for relapse?
Post-Partum Care and Support	<ul style="list-style-type: none"> • Comparative effectiveness and safety of buprenorphine management strategies after delivery <ul style="list-style-type: none"> ○ Continuing buprenorphine or replacing it with pure μ-agonists • Preventing postpartum relapse

	<ul style="list-style-type: none"> ○ What are the risk factors for relapse following delivery? ○ Do opioid type, dosing, and management strategies affect risk of relapse? • Breastfeeding <ul style="list-style-type: none"> ○ Improve prenatal education/counseling of the benefits of breastfeeding ○ What interventions could increase breastfeeding initiation rates and prolong breastfeeding duration? ○ What are the causal pathways between breastfeeding and the decreased occurrence and severity of NAS? • Contraception <ul style="list-style-type: none"> ○ How to improve access, availability, acceptance and affordability of LARC? ○ How to increase regular dual use of condoms and non-barrier methods to prevent STIs? • Post-partum Depression <ul style="list-style-type: none"> ○ What factors correlate with development of postpartum depression? ○ What are the best depression screening tools for women with substance use disorder, including frequency and timing of screening in prenatal and postpartum periods? ○ Who should be treated prophylactically to prevent post-partum depression?
Neonatal Screening and Assessment for Neonatal Abstinence Syndrome	<ul style="list-style-type: none"> • What are the best methods for identification and screening for NAS? <ul style="list-style-type: none"> ○ Need biomarker for NAS as a physiologic state e.g. epinephrine or cortisol levels for NAS ○ Need lab-on-a-chip method for rapid testing for NAS ○ What are the predictive factors for development of NAS? Diagnostic assays for who will develop NAS and how they will respond to therapies • What is the best method for assessing development of infants with NAS? <ul style="list-style-type: none"> ○ What factors most accurately define the appropriate observation period for infants at risk for NAS? How often should neonates be evaluated? ○ Develop objective tools using technology-assisted assessment ○ Individualized, comprehensive assessment to identify those infants most susceptible to poor developmental outcomes that considers: <ul style="list-style-type: none"> ■ Infant state ■ Genetic and epigenetic information ■ Pharmacologic management ■ Neurobehavioral functioning ■ Soothing techniques to avoid pharmacotherapy when possible ■ Environment ■ Adaptable for infant gestational and developmental age

	<ul style="list-style-type: none"> ○ Test scoring systems and assessment protocols against each other • What factors affect risk profiles for infants? Different substance exposures may lead to the same symptoms; need ability to distinguish them to determine best therapy. ○ Population heterogeneity ○ Dose and gestational age of exposure to maternal opioids
Treatment of Neonatal Abstinence Syndrome	<ul style="list-style-type: none"> • What is the optimal initial drug for treatment of NAS? • What are appropriate indications for a second drug? • Can genetic or epigenetic analyses be combined with antenatal exposures to tailor an optimal treatment regimen? • What is the role of poly-drug use? • What criteria best select babies and families for outpatient management? • What resources are needed for safe and effective outpatient management?
Neonatal Discharge and Follow-up	<ul style="list-style-type: none"> • What are the longer-term development outcomes for children prenatally exposed to agonist or antagonist medications? <ul style="list-style-type: none"> ○ Exposure is different based on variations in neonatal metabolism ○ No data on exposure timing and long-term developmental outcomes ○ Role of the environment is critical to outcome ○ Latent effects • How does maternal psychiatric co-morbidities and propensity for substance abuse affect child outcomes? • What are the barriers to care related to state-regulations? • Do state-specific regulations affect screening, treatment, and infant outcomes?

Table 1

Comparison of Methadone Compared With Buprenorphine Use in Pregnancy

	Methadone	Buprenorphine
Dosing	Directly observed therapy	Outpatient prescription Risk of diversion greater
First dose	20mg (oral) (range 15–30 mg)	2–4 mg (sublingual)
During withdrawal symptoms	5–10 mg every 3–6 hours Day 2: Combined total of doses given in first 24 hours	2 mg within 1–2 hours
Dose increase interval	3 days	1 day
Dose	Initial maintenance: 69 mg (range 8–160 mg) At delivery: 93 mg (range 12–185 mg)	Maintenance dose range: 8–24 mg (beyond 32 mg little increase in effect)
Half-life *	8–20 hours	30 hours
Polysubstance abuse	Preferred treatment for long-standing polysubstance abuse	May be more effective for prescription opioid users or new heroin users
Patient convenience	Less convenient – requires daily visits to federally-licensed clinic Take-home doses are allowed for Sundays or holidays unless random monthly urine drug screen is positive	More convenient – dispensed from office weekly/biweekly
Retention rates	Higher in treatment settings (78.1%)	Lower in treatment settings (57.7%)
Risk of overdose mortality	Higher, 4.18 per 1000 person years in treatment	Lower, 0.98 deaths per 1000 person years in treatment
NAS incidence **	Equal (57%)	Equal (47%)
NAS treatment duration	Longer (9.9 days)	Shorter (4.1 days)
Breastfeeding	Safe	Safe
Neurodevelopmental outcome of exposed children	No different from controls matched for age, race, and socioeconomic status	Limited evidence

* Reduced half-life as pregnancy advances

** Not statistically different